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(54) Title: COMBINATION OF AN OPIOID ANTAGONIST AND A SELECTIVE SEROTONIN REUPTAKE INHIBITOR FOR TREATMENT OF ALCOHOLISM AND ALCOHOL DEPENDENCE

(57) Abstract

The invention relates to a method of treating alcoholism and alcohol dependence in a mammal comprising administering to the mammal a therapeutically effective amount of a synergistic combination of: (i) at least one opioid antagonist, and (ii) at least one selective serotonin reuptake inhibitor. The invention also relates to compositions and kits containing the same.

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TITLE

Combination of an Opioid Antagonist and a Selective
5 Serotonin Reuptake Inhibitor for Treatment of Alcoholism
and Alcohol Dependence

FIELD OF THE INVENTION

This invention relates to a method of treating
10 alcoholism and alcohol dependence in a mammal comprising
administering to the mammal a therapeutically effective
amount of a synergistic combination of: (i) at least one
opioid antagonist, and (ii) at least one selective
serotonin reuptake inhibitor. This invention also
15 relates to compositions and kits containing the same.

BACKGROUND OF THE INVENTION

The present invention is based on an unexpected and
surprising synergy found with a combination therapy
20 involving opioid antagonists and selective serotonin
reuptake inhibitors which has been neither disclosed nor
suggested by the prior art. Such a therapy provides a
new and highly beneficial method for the treatment of
dependence.

25 Disulfiram (Antabuse®) is the only FDA approved
product that is currently available for adjunctive use
in the treatment of alcohol abuse (T. W. Rall, in:

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Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, A. G. Gilman et al., 8th Edition, Chap. 17, pp. 378-379, Pergamon Press, 1990). Disulfiram works by blocking the intermediary metabolism of alcohol. Most alcohol is normally metabolized to acetaldehyde which is further oxidized to innocuous byproducts which are excreted or recycled through energy-producing or other biosynthetic pathways. When alcohol is consumed in the presence of disulfiram, blood acetaldehyde concentrations increase to many-fold higher than normal values and produce markedly adverse behavioral and physiological responses that are collectively described as the "acetaldehyde syndrome." Psychological theory suggests that patients will avoid further consumption of alcohol to avoid these alarming and potentially life-threatening responses.

More recently, several investigators have reported that naltrexone is a useful adjunctive treatment following alcohol detoxification in alcohol-dependent human subjects (J. R. Volpicelli et al., *Arch. Gen. Psychiatry*, 49, 876, 1992; S. S. O'Malley et al., *ibid.*, 49, 881, 1992). Naltrexone blocks alcohol craving and reduces total alcohol consumption without producing mood changes or psychiatric symptoms. The authors suggest that naltrexone may be particularly useful in preventing alcohol relapse. Naltrexone, a

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well-known narcotic antagonist, is thought to work by blocking activation of the endogenous opioid reward system. Hence, naltrexone blocks the action of endorphins, enkephalins, and other endogenous opioids which may be released in response to alcohol consumption. Similar results have been obtained in studies in rats and monkeys where naltrexone, naloxone, nalmefene, and other opioid antagonists have been shown to block the apparent rewarding effects of alcohol and reduce total alcohol consumption (D. R. Brown and S. G. Holtzman, *Pharmacol. Biochem. Behav.*, 11, 567, 1979; L. D. Reid and G. A. Hunter, *Alcohol*, 1, 33, 1984; C. L. Hubbell et al., *Alcohol*, 3, 39, 1986; R. D. Myers et al., *Alcohol*, 3, 383, 1986; C. L. Hubbell et al., *Alcohol*, 8, 355, 1991; D. V. Gauvin et al., *Alcohol*, 10, 37, 1993).

Medications that enhance brain serotonergic activity have also shown effectiveness in reducing alcohol consumption and are currently under evaluation for long-term treatment of alcoholism. For example, C. A. Naranjo et al., *Clin. Pharm. Ther.*, 35, 374, 1984, and *Clin. Pharm. Ther.*, 41, 266, 1987, have shown that the serotonin uptake inhibitors citalopram and zimelidine attenuate ethanol intake in nondepressed alcohol abusers. C. L. Hubbell et al., *Alcohol*, 8, 355, 1991, demonstrated that fluoxetine, another serotonin

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uptake inhibitor, attenuates alcohol intake in rats. In a review article, C. A. Naranjo et al., J. Clin. Psychiatry, 47, 16, 1986, indicate that several serotonin uptake inhibitors including zimelidine, 5 citalopram, fluoxetine, and fluvoxamine decrease ethanol drinking in rats.

In the present invention, we demonstrate an unexpected synergistic interaction between naltrexone, an opioid antagonist, and fluoxetine, a serotonin uptake 10 inhibitor, on alcohol fluid consumption in rats. The synergism demonstrates that small combined doses of naltrexone and fluoxetine which are inactive by themselves are as effective as much higher doses of either drug alone. Alternatively, the data show that 15 the observed median effective doses (ED50 responses) for various fixed dose combinations of naltrexone and fluoxetine are significantly lower than can be accounted for by a simple additivity hypothesis. The data show that the combination of a long-lasting opioid antagonist 20 with a serotonin uptake inhibitor may provide a novel adjunctive treatment for alcohol abuse and alcoholism in man.

SUMMARY OF THE INVENTION

25 The present invention provides a method of treating alcoholism and alcohol dependence in a mammal comprising

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administering to the mammal a therapeutically effective amount of a synergistic combination of: (i) at least one opioid antagonist, such as naltrexone or nalmeferine; and (ii) at least one selective serotonin reuptake inhibitor, such as fluoxetine or paroxetine. The present invention is also directed to compositions and pharmaceutical kits containing the same. Such combination therapy provides surprisingly efficient and effective methodology for use in the treatment of alcoholism and alcohol dependence.

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DETAILED DESCRIPTION OF THE INVENTION

This present invention provides a method of treating alcoholism and alcohol dependence in a mammal comprising administering to the mammal, in combination, a therapeutically effective amount of: (i) at least one opioid antagonist; and (ii) at least one selective serotonin reuptake inhibitor.

In the present invention, it has been discovered that the administration of an opioid antagonist (component (i)) in combination with a selective serotonin reuptake inhibitor (component (ii)) may result in an unexpected synergistic effect in the reduction of alcohol consumption. Thus, the reduction in alcohol consumption when an opioid antagonist is administered in combination with a selective serotonin reuptake inhibitor may be greater than the additive effect of each agent when administered alone. This is a remarkable and unexpected effect in view of what is currently known in the literature. This synergistic combination is expected to greatly increase the efficacy of single agent or multiple agent treatments of alcoholism and alcohol dependence.

Thus, it has been discovered that an opioid antagonist may be administered in combination with a selective serotonin reuptake inhibitor, thereby reducing the doses of each drug required to achieve reduction in

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alcohol consumption. Moreover, it has been discovered that the use of the compounds of component (i) and component (ii) of the invention in combination results in a greater than additive effect. Thus, the combination treatment of the present invention of components (i), and (ii) permits the use of reduced doses of each component, with reduced adverse, toxic effects of each component. It also provides for a greater window of efficacy, since the same maximum tolerated doses can be administered before toxic effects associated with each agent are observed. A lower dosage minimizes the potential of side effects of the compounds, thereby providing an increased margin of safety relative to the margin of safety for each component when used as a single agent.

As used herein, the term "opiate antagonist" refers to compounds or compositions which serve to block the action of endogenous or exogenous opioid compounds on narcotic receptors or narcotic receptor subtypes in the brain or periphery and include naltrexone (Trexan®), naloxone (Narcan®), nalmeferene, naloxone methiodide, nalorphine, naloxonazine, naltrindole (NTI), naltrindole isothiocyanate, (NTII), naltriben (NTB), nor-binaltorphimine (nor-BNI), b-funaltrexamine (b-FNA), BNTX, cyprodime, ICI-174,864, LY117413, and MR2266. Other compounds and compositions are known and will be

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readily apparent to those skilled in the art, once armed with the present disclosure. Such opioid antagonists may serve to block the positive reinforcing effect of ethanol which results from the release of endogenous
5 opioids upon consumption of alcohol.

The phrase "selective serotonin reuptake inhibitor", as used herein, denotes compounds which enhance brain serotonergic activity by blocking the neuronal reuptake and subsequent inactivation of
10 serotonin at synaptic junctions between nerve cells. Such serotonin selective uptake inhibitor compounds include fluoxetine, sertraline, paroxetine, venlafaxine, fluvoxamine, nefazodone, citalopram, and zimeldine. Other compounds and compositions are known and will be
15 readily apparent to those skilled in the art, once armed with the present disclosure. Such selective serotonin reuptake inhibitors may serve to reduce alcohol cravings by increasing endogenous levels of serotonin.

When terms narcotic antagonist or serotonin
20 selective uptake inhibitor are used herein, it is to be understood that any of the pharmaceutically suitable salts thereof which have narcotic antagonist or serotonin uptake inhibiting properties in man and on other mammals are included by the term. Such salts
25 include the hydrochlorides, hydrobromides, hydroiodides, sulfates, bisulfates, nitrates, citrates, tartrates,

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bitartrates, phosphates, malates, maleates, fumarates, succinates, acetates, terephthalates, and pamoates.

By "therapeutically effective amount" it is meant an amount of component (i), and component (ii) that when
5 administered alone or in combination to a mammal is effective to treat alcoholism and alcohol dependence, such as by reduction of alcohol consumption and craving. Compositions of the invention present the opportunity of obtaining significant reductions in alcohol consumption
10 with reduced dosages of the narcotic antagonist and serotonin selective uptake inhibitor components, thereby diminishing the side effects and possible toxicity which would result from the otherwise required amounts of the individual drug components.

15 By "administered in combination", or the like, when referring to component (i), and component (ii), of the present invention, it is meant that the components are administered concurrently to a mammal being treated. By concurrently, it is meant that each component may be
20 administered at the same time or sequentially in any order at different points in time, however if not administered at the same time, they should be administered sufficiently closely in time so as to provide the desired treatment effect. Suitable dosing
25 intervals and dosing order with such compounds will be readily apparent to those skilled in the art, once armed

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with the present disclosure. Preferably, all components are administered at the same time, and if not administered at the same time, preferably they are all administered less than one hour apart from one another.

- 5 In a composition of the invention, naltrexone and fluoxetine are combined and have been utilized at various dose ratios based on weight of naltrexone and fluoxetine in rats offered an opportunity to drink a sweetened ethanol solution or water. The ethanol
- 10 drinking test [e.g., C. L. Hubbell et al., *Alcohol*, 3, 39, 1986] is a standard procedure for detecting and comparing the ability of different classes of compounds to increase or decrease alcohol consumption in rats and has a good correlation with the ability of compounds to
- 15 modify human alcohol drinking. Data for the rat, as presented in an isobologram, can be translated to other species where the orally effective alcohol modifying dose of the individual compounds is known or can be estimated. The method simply consists of reading the %
- 20 ED50 DOSE for each dose ratio on the best fit regression analysis curve from the rat isobologram, multiplying each component by its effective species dose, and then forming the ratio of the amount of naltrexone to fluoxetine. This basic correlation for antagonist
- 25 properties enables estimation of the range of human

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effectiveness [E. W. Pelikan, *The Pharmacologist*, 1, 73 (1959)].

Application of an equieffective dose substitution model and a curvilinear regression analysis utilizing
5 all the data for the individual compounds and various dose ratios for the combinations establishes the existence of unexpectedly enhanced alcohol drinking suppressing activity of combinations of naltrexone and fluoxetine, i.e., the resulting activity is greater than
10 the activity expected from the sum of the activities of the individual components.

The present invention also includes pharmaceutical compositions (that is, combination products), such
15 pharmaceutical compositions (combination products) comprising or consisting essentially of, in combination, an opioid antagonist (such as naltrexone), and a selective serotonin reuptake inhibitor. Such compositions may be in solid, liquid, transdermal, transnasal, or depot dosage units and may further
20 include a suitable pharmaceutical carrier.

The present invention also includes pharmaceutical kits comprising or consisting essentially of an opioid antagonist (such as naltrexone), together with a selective serotonin reuptake inhibitor. In the kit, the
25 opioid antagonist and the selective serotonin reuptake inhibitor may each be presented in separate vials as

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compounds, and/or in separate vials as compounds in combination with a pharmaceutically acceptable carrier. Alternatively, the opioid antagonist and the selective serotonin reuptake inhibitor may be combined together in one or more vials, with or without a carrier. Thus, for example, the invention includes pharmaceutical kits comprising a separate vial comprising the opioid antagonist and a separate vial comprising the selective serotonin reuptake inhibitor, each vial also containing, if desired, a carrier.

The compositions and kits of the present invention may be employed in the treatment of alcoholism and alcohol dependence.

In the method of the present invention, the opioid antagonist (such as naltrexone) may be administered in combination with a selective serotonin reuptake inhibitor to achieve a synergistic decrease in alcohol consumption. Synergy occurs when the effect (such as reduction in alcohol consumption or craving) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds.

The method of the present invention provides for an enhanced effect of the two drugs when

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administered in combination. Thus, the claimed combination treatment allows for the use of lowered clinical doses and increases the window of efficacy. In view of the marginal effects associated with the presently approved therapies for treating alcoholism and alcohol dependence, the present invention provides an important advantage over current therapies.

Opioid antagonists useful in the methods, compositions and pharmaceutical kits of the present invention include, but are not limited to naltrexone and nalmefene. These and other opioid antagonists will be readily apparent to those skilled in the art, once armed with the present disclosure.

The preparation of naltrexone is described in U.S. Patent No. 3,332,950 (H. Blumberg et al.), the disclosure of which is hereby incorporated herein by reference in its entirety. Naltrexone is available commercially as "Trexa[®]", for which product information, including dosage and administration, is given in Physicians' Desk Reference, 47th Edition, 1993, pp 956-958. The preparation of nalmefene may be carried out using preparatory methods such as those described in J. Fishman, U.S. Patent No. 3,814,768; E.F. Huhn et al., J. Med. Chem. 18, 259 (1975); P.C. Meltzer et al., European Patent Application No. 140,367 and U.S. Patent No. 4,535,157.

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Selective serotonin reuptake inhibitors useful in the method, compositions, and pharmaceutical kits of the present invention include, but are not limited to, fluoxetine, sertraline, paroxetine, venlafaxine, 5 fluvoxamine, and nefazodone. These and other selective serotonin reuptake inhibitors will be readily apparent to those skilled in the art, once armed with the present disclosure.

The preparation of fluoxetine may be carried 10 out in a number of different fashions, as will be evident to the skilled artisan. Such preparatory methods include, for example, those described in Malloy et al. GE Patent 2,500,110 and U.S. Patent 4,314,081, the disclosures of each of which are hereby incorporated 15 herein by reference in their entirety. Fluoxetine is available commercially as "Prozac®", for which the product information, including dosage and administration, is given in Physicians' Desk Reference, 48th Edition, 1994, pp. 877-880. The preparation of 20 sertraline may be carried using preparatory methods such as those described in initials Welch, et al. European Patent Application 30,081 and U.S. Patent No. 4,536,518, the disclosures of each of which are hereby incorporated herein by reference in their entirety. Sertraline 25 hydrochloride is available commercially as "Zoloft®", for which the product information, including dosage and

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administration, is given in Physicians' Desk Reference, 48th Edition, 1994, pp. 2000-2003.

In the present invention it has been found that therapeutic agents of component (i), and component
5 (ii) described above, when administered in combination, exert a synergistic effect, particularly, reducing the consumption of alcohol. Such combination treatment may allow the use of lowered clinical doses with increase efficacy and a wider safety window.

10 Component (i) of the present invention may also be provided as a pharmaceutical composition comprising an therapeutically effective amount of an opioid antagonist and a pharmaceutically acceptable carrier. Component (ii) of the present invention may
15 likewise be presented as a pharmaceutical composition comprising a therapeutically effective amount of a selective serotonin reuptake inhibitor and a pharmaceutically acceptable carrier. Mixtures of the components (i), and (ii) with or without a
20 pharmaceutically acceptable carrier, are also within the ambit of the present invention.

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Dosage and Formulation

The opioid antagonist (component (i)), and selective serotonin reuptake inhibitor (component (ii)) combination treatment of the invention can be administered by any conventional means available for the use in conjunction with pharmaceuticals, either as individual separate dosage units administered simultaneously or concurrently, or in a physical combination of each component therapeutic agent in a single or combined dosage unit. The active agents can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will, of course vary depending on the use and known factors such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. The recipient may be any type of mammal, but is preferably a human.

For use in the treatment of diseases characterized by abnormally high consumption of alcohol, by way of general guidance, a daily oral dosage of active ingredient(s) can be about 0.001 to 1000 mg/kg of

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body weight. Ordinarily a dose of 0.1 to 500 mg/kg per day in divided doses one to four times a day or in sustained release form is effective to obtain the desired results.

5 The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be
10 administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

15 In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as carrier materials) suitably selected with respect to the
20 intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be
25 combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch,

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sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn-sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

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Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, 5 polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful 10 in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and 15 crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (compositions) suitable for administration contain about 1 milligram to 100 milligrams of active ingredient per unit. In these 20 pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient may be administered orally in solid dosage forms, such as capsules, tablets, 25 and powders, or in liquid dosage forms, such as elixirs,

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syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfate, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents.

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Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

- 5 Suitable pharmaceutical carriers and methods of preparing pharmaceutical dosage forms are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

- 10 Useful pharmaceutical compositions (dosage forms) for administration of the compounds of this invention can be illustrated as follows:

Capsules

- 15 A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

20 Soft Gelatin Capsules

- A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.
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Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

10 Suspension

An aqueous suspension is prepared for oral administration so that each 5 ml contain 25 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mg of vanillin.

Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is sterilized by commonly used techniques.

Each therapeutic agent component of this invention can independently be in any dosage form, such as those described above, and can also be administered in various ways, as described above. The component (i), and (ii) of the invention may be formulated together, in a single

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dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.) as a composition (combination product). When component (i), and (ii) are not formulated together in a single dosage unit, the

5 opioid antagonist component (i) may be administered at the same time as the selective serotonin reuptake inhibitor component (ii) or in any order. For example, component (i) of this invention may be administered first, followed by administration of component (ii), or

10 they may be administered in the reverse order. When not administered at the same time, preferably the administration of component (i) and component (ii) of this invention occurs less than about one hour apart. Preferably, the route of administration of component (i)

15 and component (ii), of the invention is oral. The terms oral agent, oral release enhancer, oral compound, or the like, as used herein, denote compounds which may be orally administered. Although it is preferable that component (i), and (ii), of the invention are both

20 administered by the same route (that is, for example, both orally) or in the same dosage form (that is, for example, as a tablet), if desired, they may each be administered by different routes (that is, for example, one component of the combination product may be

25 administered orally, and another component may be administered intravenously) or in different dosage forms

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(that is, for example, one component as a tablet and another as a liquid).

As will be appreciated by a medical practitioner skilled in the art, the dosage of the combination
5 therapy of the invention may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the
10 kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

The proper dosage of component (i), and component (ii) in this invention will be readily ascertainable by a medical practitioner skilled in the art, based upon
15 the present disclosure. By way of general guidance, typically a daily dosage may be about 10 milligrams to about 1.5 grams of each component. By way of general guidance, when the compounds of component (i) and component (ii) are administered in combination, the
20 dosage amount of each component may be reduced by about 70-80% relative to the usual dosage of the component when it is administered alone as a single agent for the treatment of alcoholism and alcohol dependence, in view of the synergistic effect of the combination.

25 The combination products of this invention may be formulated such that, although the active ingredients

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are combined in a single dosage unit, the physical contact between the active ingredients is minimized. In order to minimize contact, for example, where the product is orally administered, one or more of the

5 active ingredients may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the

10 gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. Another embodiment of this invention where oral administration is desired provides for a combination product wherein one or more of the active

15 ingredients is coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released

20 component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one or more components is coated with a sustained and/or

25 enteric release polymer, and the other(s) component is also coated with a polymer such as a low viscosity grade

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of hydroxypropyl methylcellulose or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with
5 the other component.

Dosage forms of the combination products of the present invention wherein one active ingredient is enteric coated can be in the form of tablets such that the enteric coated component and the other active
10 ingredients are blended together and then compressed into a tablet or such that the enteric coated component is compressed into one tablet layer and the other active ingredient is compressed into an additional layer. Optionally, in order to further separate the two layers,
15 one or more placebo layers may be present such that the placebo layer is between the layers of active ingredients. In addition, dosage forms of the present invention can be in the form of capsules wherein one active ingredient is compressed into a tablet or in the
20 form of a plurality of microtablets, particles, granules or non-perils, which are then enteric coated. These enteric coated microtablets, particles, granules or non-perils are then placed into a capsule or compressed into a capsule along with a granulation of the other
25 active ingredient.

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These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time or concurrently by the same manner, will be readily apparent to those skilled in the art, based on the present disclosure.

Pharmaceutical kits useful for the treatment of alcoholism and alcohol dependence, which comprise a therapeutically effective amount of a compound of component (i), and a compound of component (ii), in one or more containers, are also within the ambit of the present invention. Sterilization of the container may be carried out using conventional sterilization methodology well known to those skilled in the art. Component (i), and component (ii) may be in the same container or in separate containers. The containers of materials may comprise separate containers, or one or more multi-part containers, as desired. Component (i), and component (ii), may be separate, or physically combined into a single dosage form or unit as described above. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as for example, one or more pharmaceutically acceptable carriers, additional vials for mixing the components, etc., as will be readily

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apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

Examples

The examples described below may be used to demonstrate the synergistic effect of an opioid antagonist, such as naltrexone, administered in combination with a selective serotonin reuptake inhibitor. The tests described below demonstrate that a representative opioid antagonist, naltrexone, acts synergistically with a representative selective serotonin reuptake inhibitor, fluoxetine, resulting in reduction of total alcohol consumption in a model of sustained ethanol drinking behavior in rats

Protocol

The methods for testing individual compounds for their ability to modify alcohol intake are essentially the same as described by C. L. Hubbell *et al.* in *Alcohol*, 3, 39 (1986). Male Sprague-Dawley rats are obtained from Charles River Breeding Laboratories. For 14-30 days, rats are given a 2 hour daily opportunity to drink a sweetened 10-20% ethanol solution or water.

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Rats are deprived of water for the remaining 22 hours each day. Rats eventually drink considerable amounts of ethanol solutions equivalent to about 1.0 to 3.0 g/kg of pure ethanol equivalent each day. After stable levels of alcohol intakes are achieved, various pharmacological preparations are tested for their effects on the intake of sweetened alcohol solutions. For the next few days, designated groups of rats are administered various oral doses of naltrexone, fluoxetine, fixed-dose combinations of naltrexone and fluoxetine, or water (vehicle) 10-30 minutes before their opportunity to drink ethanol solutions. In similar experiments, data may also be obtained using rats prepared by the "Samson" sucrose-fading procedure (D. V. Gauvin et al., *Alcohol*, 10, 37, 1993). In this procedure, rats are offered a 30 minute opportunity to drink sweetened ethanol solutions each day and are not water deprived for the remaining period each day. To induce a stable level of alcohol consumption, the concentration ratios of the sucrose-ethanol solutions are varied over days by increasing the ethanol concentration from 5% to 20% w/v and reducing, eventually to zero, the sucrose concentration. On day 1 only, rats are deprived of water for 16 hours prior to the introduction of 20% sucrose solutions. Thereafter, access to food and water is ad libitum except during the 30 minute ethanol-sucrose access test period each day.

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Rats are eventually maintained on 20% ethanol solutions during the daily test period. Test compounds are administered as described above.

All rats are dosed sequentially by the oral route with solutions or suspensions of naltrexone HCl and/or of fluoxetine HCl. A dosing volume of 1 to 10 ml/kg is used for each sequential solution or suspension. All doses are coded and the test is performed under a code not known to the observer.

10

Statistics

The data for each experimental group are from 3-7 separate studies. The reduction in alcohol consumption is quantified by determining the dosage of individual drugs or fixed-dose drug combinations which reduce alcohol consumption by 50% from pre-drug values for each rat or each group of rats. This dosage as described herein is referred to as the ED50 dose. All ED50 values and their 95% confidence limits are determined numerically by the computer-assisted methods of Finney [D. J. Finney, "Probit Analysis," Third Edition, Cambridge University Press, Cambridge, England, 1971], Tallarida and Murray [R. J. Tallarida and R. B. Murray, "Manual of Pharmacologic Calculations with Computer

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Programs," Second Edition, Springer-Verlag, New York, 1987], or Litchfield and Wilcoxon (J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, 96, 99, 1949).

5 The nature of the interaction (addition, potentiation, or antagonism) is determined by graphing the results in a Loewe isobologram (S. Loewe, *Pharm. Rev.*, 9, 237, 1957). Regression analysis is used to evaluate the statistical significance of the isobologram
10 using an equi-effective dose substitution model (Appendix II). All tests of statistical significance are carried out at a 95% confidence level ($P \leq 0.05$).

 The isobologram is a quantitative method for measuring interactions between drugs where dose-effect
15 relationships are depicted in a multi-dimensional array with lines connecting dose pairs that are equieffective in relationship to a common pharmacological endpoint. In this instance, the alcohol drinking test is used to estimate a common level of suppressant activity for the
20 two component drugs separately and for each fixed dose-ratio combination. In the isobolographic figure, areas of dose addition, synergism, and/or antagonism are clearly defined by reference to the theoretical "ED50 Addition Line." According to Loewe's isobolographic
25 theory, ED50's falling under the curve (between the ED50 Addition Line and the origin) would represent

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unexpectedly enhanced suppressant activity and combination ED50's located above the line would represent unexpectedly diminished suppressant activity.

Most importantly, the isobolographic technique
5 permits a full range of doses and dose combinations to be examined where the proportion of the first drug to the second actually varies from 0 to infinity, and to determine, by virtue of the graphical display, whether
10 any one or more of the paired drug combinations displays unique pharmacological properties in comparison to the entire body of data generated. The isobologram is also valuable for organizing the data in a form which is easily amenable to statistical assessment of observed differences.

15 The nature of the interaction (addition, potentiation, or antagonism) between naltrexone and fluoxetine is determined by graphing equi-effective (ED50) amounts of naltrexone alone, fluoxetine alone, and of each fixed-dose combination in a Loewe
20 isobologram (S. Loewe, *Pharm. Rev.*, 9, 237, 1957). Regression analysis is used to evaluate the statistical significance of the isobologram using an equi-effective dose substitution model. The effects of two compounds are additive if the response to a dose of the two in
25 combination does not change when a portion of one is removed from the mixture and replaced by an equipotent

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portion of the other. If such substitution increases the response, the mixing together of the compounds is said to potentiate their effect.

Consider ED50 doses of mixtures of X units of compound B with Y units of compound A, whose ED50 doses are b and a, respectively. Given the hypothesis of additivity, all doses of mixtures satisfying the straight line relation,

10

$$(1) \quad Y = a - \frac{a}{b} X$$

will be ED50 doses. To test the hypothesis of additivity, ED50 doses of mixtures are estimated through probit analysis of data from experiments run at various
15 ratios of A to B. Linear and curvilinear regression models are fitted to the data to estimate the amounts of A in respective ED50 doses, given the amount of B, (or, conversely, the amount of B, given A). If a curvilinear regression fits the data significantly better than a
20 straight line regression, the hypothesis of additivity is refuted and potentiation exists.

Values of Y calculated from the straight line of Equation 1, and values of Y calculated from the curvilinear regression are plotted against X on an ED50
25 isobologram to describe the potentiation response.

It is convenient to standardize the units of dose such that 100 units of either compound alone is its

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respective estimated ED50 dose. The additivity hypothesis, then, will be represented by a straight line from 100 on the Y-axis to 100 on the X-axis on the isobologram, and Equation (1) becomes:

5

$$Y = 100 - X.$$

The regression is fitted to the data by the method of least squares. Residual squared deviations about the line of best fit are minimized in directions along lines from the origin through respective data points on the isobologram, these lines making angles with X-axis, $\tan^{-1}(Y/X)$. This is accomplished by a transformation prior to the regression analysis. Its inverse is applied to transform the coordinates of the regression curve back to the X,Y coordinates of the isobologram.

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15
20

Let D_r be an ED50 dose of a mixture of A and B, where r is the fraction of compound B in the mixture; i.e.

$$r = \frac{X}{X + Y}.$$

It follows from Equation 1 that

25

$$D_r = \frac{\alpha\beta}{\alpha r + \beta(1-r)}.$$

From the additivity hypothesis, the logarithms of the ED50 doses at various mixture ratios are a straight line function of $(\log D_r)$. To test the hypothesis,

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polynomial regressions, as follows, are fitted to ED50 estimates from experimental data obtained at various mixture ratios:

$$5 \quad (2) \quad F_r = \log D_r = b_0 + \sum_{i=1}^K b_i \left\{ \log \left[\frac{\alpha\beta}{\alpha r + \beta(1-r)} \right] \right\}^i.$$

The additivity hypothesis is refuted if a polynomial of degree higher than one fits the data significantly better than the straight line equation:

$$10 \quad F_r = b_0 + b_1 \left[\log \left(\frac{\alpha\beta}{\alpha r + \beta(1-r)} \right) \right].$$

15

Since X and Y are uniquely determined by F_r and r , the coordinates of the regression are transformed readily to the coordinates of the isobologram.

If data are scaled to ED50 dose levels of 100 standard dose units, Equation (2) becomes

$$(2.1) \quad F_s = \log 100 = 2.$$

25

The additivity hypothesis implies that F_s is independent of r_s , and may be tested by analysis of the regression model

$$(2.2) \quad F_s = b_0 + \sum_{i=1}^K b_i r_s^i.$$

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the subscripts, s, indicating that the data are scaled. A statistically significant regression will refute the hypothesis.

The model of least squares utilizes jointly the
5 information contained in all of the separate data points. Statistical significance of the curvilinearity of the regression model establishes the existence of potentiation (or antagonism) of the compounds in the biological system studied. The parameters in the model
10 describe its intensity over the range of mixture ratios, from 0 to 1, the nature of which is seen readily when the regression is plotted on the isobologram. This method is used to determine the best-fitting ED50 regression line through ED50 data points representing
15 equivalent levels of alcohol suppressing activity for each of the naltrexone-fluoxetine dose-ratios and for naltrexone and fluoxetine alone. As shown in an isobologram plot, the calculated quadratic polynomial "ED50 Regression Line" fits the data significantly
20 better than the straight "ED50 Addition Line" using stringent 95% confidence limits. Thus, consistent with Loewe's isobolographic model, the hypothesis of additivity is refuted and potentiation of alcohol drink suppressing activity is established for all combinations
25 of naltrexone and fluoxetine.

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Results

The results demonstrate that groups of rats receiving effective doses of naltrexone or fluoxetine each consume significantly less ethanol on each day tested compared to vehicle-treated rats. Effective oral doses of naltrexone generally range from 0.1 to 10 mg/kg and effective doses of fluoxetine generally range from 1 to 100 mg/kg. In rats administered fixed-dose combinations of naltrexone and fluoxetine, ethanol drinking is significantly reduced using lower doses of naltrexone and fluoxetine than represented by their individual proportions in the fixed-dose mixture, hence a synergistic interaction exists between naltrexone and fluoxetine which produces a greater reduction in alcohol consumption than can be accounted for based on addition of their individual effects.

The disclosures of all of the references cited herein are hereby incorporated herein by reference in their entirety.

Various modifications of the invention in addition to those shown and described herein will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

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CLAIMS

WHAT IS CLAIMED IS:

- 5 1. A method of treating alcoholism and alcohol dependence comprising administering to a mammal a therapeutically effective amount of a synergistic combination of: (i) at least one opioid antagonist; and (ii) at least one selective serotonin reuptake inhibitor.
- 10 2. A method of Claim 1 wherein said opioid antagonist is selected from the group consisting of naltrexone, nalmeferene, and naloxone.
- 15 3. A method of Claim 2 wherein said opioid antagonist is naltrexone.
- 20 4. A method of Claim 1 wherein said selective serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, and nefazodone.
- 25 5. A method of Claim 1 wherein said selective serotonin reuptake inhibitor is fluoxetine, sertraline, paroxetine, or fluvoxamine.

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6. A method of Claim 1 wherein said selective serotonin reuptake inhibitor is fluoxetine.

7. A method of Claim 1 wherein said selective serotonin reuptake inhibitor is paroxetine.

8. A method of Claim 1 wherein said opioid antagonist is naltrexone and said selective serotonin reuptake inhibitor is fluoxetine.

10

9. A method of Claim 1 wherein said opioid antagonist is naltrexone and said selective serotonin reuptake inhibitor is paroxetine.

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10. A method of Claim 1 wherein said mammal is a human.

11. A method of Claim 2 wherein said mammal is a human.

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12. A method of Claim 1 wherein said administration is oral.

13. A method of Claim 2 wherein said administration is oral.

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14. A pharmaceutical composition comprising a therapeutically effective amount of a synergistic combination of: (i) at least one opioid antagonist; and (ii) at least one selective serotonin reuptake inhibitor.

15 15. A pharmaceutical composition of Claim 14 wherein said opioid antagonist is selected from the group consisting of naltrexone, nalmeferene, and naloxone.

16 16. A pharmaceutical composition of Claim 14 wherein said opioid antagonist is naltrexone.

17 17. A pharmaceutical composition of Claim 14 wherein said selective serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, and nefazodone.

20 18. A pharmaceutical composition of Claim 14 wherein said selective serotonin reuptake inhibitor is fluoxetine, sertraline, paroxetine, or fluvoxamine.

25 19. A pharmaceutical composition of Claim 14 wherein said selective serotonin reuptake inhibitor is fluoxetine.

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20. A pharmaceutical composition of Claim 14 wherein said selective serotonin reuptake inhibitor is paroxetine.

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21. A pharmaceutical composition of Claim 14 wherein said opioid antagonist is naltrexone and said selective serotonin reuptake inhibitor is fluoxetine.

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22. A pharmaceutical composition of Claim 14 wherein said opioid antagonist is naltrexone and said selective serotonin reuptake inhibitor is paroxetine.

15

23. A pharmaceutical kit comprising: (i) at least one opioid antagonist; and (ii) at least one selective serotonin reuptake inhibitor.

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24. A pharmaceutical kit of Claim 23 wherein said opioid antagonist is selected from the group consisting of naltrexone, nalmeferene, and naloxone.

25

25. A pharmaceutical kit of Claim 23 wherein said opioid antagonist is naltrexone.

26. A pharmaceutical kit of Claim 23 wherein said selective serotonin reuptake inhibitor is selected from

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the group consisting of fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, and nefazodone.

27. A pharmaceutical kit of Claim 23 wherein said
5 selective serotonin reuptake inhibitor is fluoxetine, sertraline, paroxetine, or fluvoxamine.

28. A pharmaceutical kit of Claim 23 wherein said
selective serotonin reuptake inhibitor is fluoxetine.

10

29. A pharmaceutical kit of Claim 23 wherein said
selective serotonin reuptake inhibitor is paroxetine.

30. A pharmaceutical kit of Claim 17 wherein said
15 opioid antagonist is naltrexone and said selective serotonin reuptake inhibitor is fluoxetine.

31. A pharmaceutical kit of Claim 23 wherein said
opioid antagonist is naltrexone and said selective
20 serotonin reuptake inhibitor is paroxetine.

32. A pharmaceutical kit of Claim 23 further
comprising conventional kit components.

25 33. A pharmaceutical kit of Claim 30 further
comprising conventional kit components.

INTERNATIONAL SEARCH REPORT

 Int. Application No
 PCT/US 95/10987

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/485 //(A61K31/485,31:445),(A61K31/485,31:135)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A, 94 20100 (NAGLE JOHN S ; DANTE LEE G (US)) 15 September 1994	14-19, 21, 23-28, 32, 33 1-13
Y	see abstract see page 5, line 13-23 ---	
Y	MED. HYG., 12 JAN 1994, 52/2008 (93-96), SWITZERLAND, FERRERO F. ET AL 'Psychiatry' see page 95, column 3, paragraph 2-4 ---	1-13
X	J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY, 1993, 32/4 (870-873), USA, BENJAMIN E. ET AL 'Naltrexone and fluoxetine in Prader-Willi syndrome' see abstract --- -/-	14-19, 21, 23-28, 30-33

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 "A" document member of the same patent family

Date of the actual completion of the international search

7 February 1996

Date of mailing of the international search report

28. 02. 96

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+ 31-70) 340-2060, Tx. 31 651 epo nl,
 Fax: (+ 31-70) 340-3016

Authorized officer

Leherste, C

INTERNATIONAL SEARCH REPORT

Application No
PCT/US 95/10987

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PSYCHIATR. CLIN. NORTH AM., 1993, 16/4 (679-692), USA, BOHN M.J. 'Alcoholism' see page 687, paragraph 3 see page 688, paragraph 2 see page 690, paragraph 2-3 ---	1-13
A	WO,A,92 19226 (DYNAGEN INC) 12 November 1992 see abstract see claim 43 -----	1-33

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 95/10987

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ **Claims Nos.:**
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-13 are directed to a method of treatment of
(diagnostic method practised on) the human/animal body the search has been
carried out and based on the alleged effects of the compound/composition.
2. ☐ **Claims Nos.:**
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. ☐ **Claims Nos.:**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/US 95/10987

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9420100	15-09-94	AU-B- 6517494 CA-A- 2157475 EP-A- 0687175	26-09-94 15-09-94 20-12-95
WO-A-9219226	12-11-92	AU-B- 657973 AU-B- 2016092 AU-B- 2154892 CA-A- 2102507 HU-A- 69390 JP-T- 6507416 NO-A- 933971 WO-A- 9219241 US-A- 5403595 US-A- 5486362	30-03-95 21-12-92 21-12-92 08-11-92 28-09-95 25-08-94 07-01-94 12-11-92 04-04-95 23-01-96